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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/096,749	06/12/98	KOIDE S	109.034US1

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EXAMINER	
HELMS, L	
ART UNIT	**PAPER NUMBER**
1642	11

DATE MAILED: 08/18/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/096,749	Kolde et al
Examiner	**Group Art Unit**
Larry R. Helms Ph.D.	1642

☒ Responsive to communication(s) filed on *13 Jun 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-39* is/are pending in the applicat

Of the above, claim(s) *7-39* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-6* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5 and 8*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's election without traverse of Group I, Claims 1-6 in Paper No. 10 is acknowledged.

2. Claims 7-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Election was made **without** traverse in Paper No. 10.

3. Claims 1-6 are pending and under examination.

Information Disclosure Statement

4. The IDS filed 2/17/99 as paper # 5 has been considered, however, the reference of Koide et al is incomplete. The reference lacks the journal, date, and page number for the reference. If Applicants would submit this information the Examiner will complete the IDS.

Specification

5. The disclosure is objected to because of the following informalities:

a. The first line of the specification should be updated to indicate that the instant application is claiming benefit from provisional application 60/049,410, filed 06/12/97.

b. The use of the apparent trademarks "Sephacryl S 100HR" and "ResourceS" column on page 23, for examples, have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

c. The Brief Description of the Drawings for Figures 1, 3, 4, 15, need to have separate descriptions for each view.

Appropriate correction is required.

Drawings

6. The drawings are objected to because Figures 2, 3, 7, 8, 9, 10, should be on separate pages. Correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-6 are indefinite for reciting "plurality of Fn3.... linked to a plurality of loop region sequences" in claim 1 for the exact meaning of the phrase is not clear. It is not clear how many beta-strands and loop regions are encompassed by the claims.

b. Claims 1-5 are indefinite for reciting "deletion, insertion, or replacement of at least two amino acids" in claims 1 and "deletion or replacement of at least 2 amino acids" in claim 5 for the exact meaning of the phrases are unclear. Does the phrase mean that all amino acids can be replaced or deleted?

DKOP

c. Claim 4 recites the limitation "one or more of the loop regions" in claim 1. There is insufficient antecedent basis for this limitation in claim 1.

d. Claims 2 and 3 are indefinite for reciting "capable" for the exact meaning of the term is not clear. Does the loop region bind a specific binding partner in claim 2 and does the loop region catalyze a chemical reaction or not?

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for A fibronectin type III polypeptide monobody comprising the tenth fibronectin unit of human fibronectin wherein the monobody loop regions of residues 22-30 in the BC loop and residues 76-87 in the FG loop vary by substitutions, insertions, or replacement

from the wild-type FN3 by 3 to 25 amino acids, wherein the replaced loop region amino acid residues bind to a specific binding partner and do not affect the proper folding of the monobody, does not reasonably provide enablement for a fibronectin type III polypeptide monobody comprising a structure of less that the FN3 domain or wherein any amino acids in any loop region other than the BC or FG loops have any amino acid deletions, insertions, or replacements or wherein the beta-strand domains have 50% sequence homology to the wild-type beta-strand domain or wherein any loop region is capable of catalyzing a chemical reaction such that the ratio of kcat/kuncat is greater that 10. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

a. Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

b. The claims are broadly drawn to a monobody comprising part of the FN3 domain or a FN3 domain with amino acids replaced with any amino acids in the beta-strand domain, or beta-strand domains that are 50% homologous to the wild-type FN3 domain, or deletions, insertions,

or replacements of any amino acid residue in any of the loops, wherein the monobody would not bind a specific partner or would not properly fold or would not have a specific function. The claims also encompass a loop replacement wherein the loop region catalyzes a chemical reaction with a kcat/kuncat of greater that 10 which encompasses kcat/kuncat of 100, 1000, and 100K. In addition, claims 1 and 5 encompass a monobody with all of the amino acids replaced from that of the wild-type loop region sequences.

c. The specification teaches the tenth FN3 domain from fibronectin and amino acid substitutions, replacements, or insertions in the loop regions of loops BC and FG (see pages 18, lines 20-22, page 20, line 10, page 38-39, Example X, XII). The specification teaches that the Ubi4 protein, which is a ubiquitin binding scaffold had significantly reduced solubility as compared to wild type (see page 56, lines 18-19). The specification also teaches the NMR spectroscopy of Ubi4-Fn3 which indicated that the protein retains the global fold of Fn3 (see page 58, lines 9-19). The specification fails to disclose replacements, insertions, or deletions in any other loops other than BC and FG. The specification fails to enable a monobody with a loop region that catalyzes a chemical reaction with a kcat/kuncat of 10 or greater than 10. The specification fails to enable a monobody with beta-strand domains of at least 50% homology to the amino acid sequence of the wild-type beta-strand domain sequences.

d. The claims are not commensurate in scope with the enablement provided in the specification. The claims encompass replacement of any loop regions in the Fn3 monobody. As evidenced by Helms et al (Protein Science 4:2073-2081, 1995) the replacement of any loop as

well as the replacement of any amino acid residues from 2-12 residues in the loop of an immunoglobulin domain can lead to deleterious effects on stability of the protein domain. As stated in Helms et al "It is generally believed that loop regions in globular proteins, and particularly hypervariable loops in immunoglobulins, can accommodate a wide variety of sequence changes without jeopardizing protein structure or stability. We show here, however, that novel sequences introduced within complementarity determining regions (CDRs) 1 and 3 of the immunoglobulin variable domain REI VL can significantly diminish the stability of the native state of this protein." (See abstract and entire document). As stated in the specification the Fn3 monobody "has a fold similar to that of immunoglobulin domains" (see page 18, lines 20-21) and as such one skilled in the art would reasonably conclude from Helms et al that not every loop replacement will result in a correctly folded protein wherein the loop region would bind to a specific binding partner.

e. The claims encompass a protein with 50% homology in the beta-strand domain as compared to wild-type Fn3 or a protein with any number of amino acid deletions, insertions, or replacements in the loops. Protein chemistry is probably one of the most unpredictable areas of biotechnology and as such it is unpredictable what the outcome of replacements will be or if a protein with 50% homology will function as claimed or be structurally related. The replacements can have effects on activity as well as global folding of the polypeptide. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the

protein (see Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252).

f. Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin. Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase. Lin et al Biochemistry USA Vol 14:1559-1563 (1975).

g. These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein.

h. Although biotechnology has made great strides in the recent past, these references serve to demonstrate exactly how little we really know about the art. Elucidation off the genetic code induces one to believe that one can readily obtain a functional synthetic protein for any known nucleic acid sequence with predictable results. The results of the construction of synthetic proteins remain very unpredictable as Burgess et al, Lazar et al, Schwartz et al, and Lin et al ~~and Acland et al~~ conclusively demonstrate.

RH 7/27/00

I. As evidenced by Helms et al, Burgess et al, Lazar et al, Schwartz et al, Lin et al and ~~Acland et al~~ and in view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad of monobodies encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1-6 are rejected under 35 U.S.C. 102(a or b) as being anticipated by Koide et al (IDS # 5). If the date of the reference is less than a year of 6/12/97 then the rejection is a 102(a), if the reference is more than a year of 6/12/97 then the rejection is a 102(b).

a. The claims recite a fibronectin type III monobody comprising a plurality of Fn3 beta-strand domain sequences that are linked to a plurality of loop region sequences wherein one or more of the loop region sequences vary by deletion, insertion or replacement of at least two amino acids or insertion of 3-25 amino acids from the corresponding loop region sequences in wild-type and wherein the beta-strand domain of the monobody is at least 50% homologous to

the wild-type Fn3 domain sequence wherein one or more loop regions is capable of binding a specific binding partner, wherein the loop region is capable of catalyzing a chemical reaction, and wherein the loop regions comprise the BC or FG loops.

b. Koide et al teach a monobody scaffold comprising the Fn3 domain in which two loop regions were randomized with amino acid residues and the monobodies bind a specific target molecule with significant affinities to target molecules. Koide et al is silent as to the number of amino acid residues replaced but it would be inherent that at least two to three amino acid residues would be replaced in order to obtain "significant affinities".

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

14. Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Main et al (Cell 71:671-678, 1992, IDS #5 and further in view of Lee et al (Protein Engineering 6:745-754, 1993, IDS # 8).

a. The claims have been described supra.

b. Main et al teach the structure of the tenth fibronectin type III domain which contains an RGD recognition site in loop FG which is solvent exposed and highly mobile (see abstract). Main et al also teach that the topology is similar to that of immunoglobulin C domains and the FG loops have similar topology (see Figure 5 and page 675). Main et al also teach "The structure presented in this paper gives insight into the way a functional loop can be built onto a structural framework and, by virtue of its flexibility, be able to perform a wide range of functions." (See page 676). Main et al does not teach replacements of amino acid residues from 2 or 3-25 in the Fn3 domain loops and producing a loop with binding to a specific binding partner. These deficiencies are made up for in the teachings of Lee et al.

c. Lee et al teach the immunoglobulin VL domain as a protein scaffold for insertion of amino acid sequences into the CDR loops in the protein to produce a protein which specifically binds to a binding partner (see abstract). Lee et al also teach the affinity constant for the binding of the proteins to the receptor is less than 10^{-6} moles/liter (see Table I). Lee et al also teach

"Scaffolds capable of displaying more than one sequence might be used to construct multifunctional molecules as well as reconstruct discontinuous binding surfaces" (see page 753).

d. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the fibronectin type III domain as taught by Main as a scaffold for replacement of amino acid residues as taught by Lee et al.

g. One of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have used the fibronectin type III domain as taught by Main et al as a scaffold for replacement of amino acid residues as taught by Lee et al because Main et al teach that the fibronectin type III topology is similar to that of immunoglobulins and functional loops can be built onto a structural framework to be able to perform a wide range of functions. In addition, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have used the fibronectin type III domain as taught by Main et al as a scaffold for replacement of amino acid residues as taught by Lee et al because Lee et al teach replacement of surface loops with amino acid sequences that bind to a receptor in an immunoglobulin domain with affinity in the nanomolar range. Moreover, one of ordinary skill in the art would have known that the FG loop of Fn3 has similar topography as CDR3 in an immunoglobulin (see figure 5 in Main et al) and both of these loops are surface exposed and it would have been obvious to replace residues in the FG loop in Fn3 because Lee et al replaced residues in the CDR3 of REI which is also a surface exposed loop. Thus, it would have been obvious to one of ordinary skill in the art to use the Fn3 domain of Main et al, which has a fold

similar to the immunoglobulin of Lee et al, and replace residues in the surface exposed loops with residues that would bind to a binding partner as taught by Lee et al .

h. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusions

15. No Claims are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

17. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official

Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

SHEELA HUFF
PRIMARY EXAMINER